Hereditary Haemorrhagic Telangiectasia in Children. Endovascular Treatment of Neurovascular Malformations

Results in 31 Patients

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Summary

Hereditary haemorrhagic telangiectasia (HHT) is a heterogeneous disease that may present with different clinical phenotypes and different clinical expressions. Concerning the neurovascular expressions of this disease, the paediatric age group in particular presents with potentially devastating symptomatic phenotypes. The purpose of this article was to review the therapeutic results of endovascular treatment of neurovascular malformations in children.

A total of 31 children under the age of 16 were included in this retrospective analysis. All children were treated in a single centre. Twenty children presented with 28 arteriovenous (AV) fistulae including seven children with spinal AV fistulae and 14 children with cerebral AV fistulae (one child had both a spinal and cerebral fistulae). Eleven children had small nidus type AV malformations. All embolizations were performed in a single centre employing superselective glue injection. Follow-up ranged between three and 168 months (mean: 66 months)

A total of 115 feeding vessels were embolized in 81 single sessions resulting in a mean overall occlusion rate of the malformation of 77.4% (ranging from 30 to 100%). Two of 30 patients (6.5%) died as a direct complication of the embolization procedure, two patients (6.5%) had a persistent new neurological deficit, eight patients (26.7%) were clinically unchanged following the procedure. In 11 patients (36.7%) an amelioration of symptoms but no cure could be achieved, six patients (20%) were completely asymptomatic following the endovascular procedure. In the surviving patients morphological complete occlusion was possible in twelve patients (38%), therapy is still not complete in six patients.

Since the natural history of neurovascular manifestations of HHT in children is associated with a high morbidity and mortality, therapeutic intervention is mandatory. In most instances a morphological target can be identified, therefore even partial and staged treatment can be performed. Our results demonstrate that in 27/31 patients these targeted interventions resulted in stabilizing the disease, ameliorating the symptoms or even in curing the patient. The endovascular approach employing glue as the embolizing agent represents therefore a safe and efficient way to control the neurovascular phenotypes of HHT.

Introduction

Hereditary haemorrhagic telangiectasia (HHT, Rendu-Osler-Weber disease) is an autosomal dominant vascular dysplasia with a high penetrance but variable expressivity. HHT can no longer be regarded as a rare disease as recent epidemiological surveys suggest an incidence

of HHT of one in five–10.000 [1,2,3]. Mutations in two different genes have been deemed responsible for HHT, most cases being caused by mutations in the endoglin gene on chromosome 9q or the activin receptor-like Kinase 1 (ALK-1) gene on chromosome 12q. However, a third location on a yet unknown locus must be taken into consideration since some patients with the classical signs of HHT test negative for both the endoglin gene and the ALK-1 gene defect. Both endoglin and ALK1 play distinct roles in the transforming growth factor-beta (TGF-ß) signalling pathway. TGF-ß1 is amongst others a potent angiogenic factor and mediator of vascular remodelling as it controls extracellular matrix production by endothelial cells, smooth muscle cells and pericytes [4]. Both ALK 1 and endoglin are expressed primarily in endothelial cells [5], and both can bind TGF-ß1 molecules to influence the process of angiogenesis. Endothelial cells lacking functioning endoglin or ALK 1 show an altered response to TGF-ß1 and therefore form abnormal vessels and abnormal connections between vessels [4] resulting in vascular malformations that may occur in multiple organs including the lung, liver, gastrointestinal tract, skin or central nervous system (CNS). Diagnosis of HHT is based on the four Curaçao criteria of a) spontaneous recurrent nosebleeds, b) mucocutaneous telangiectasia at characteristic sites (lips, oral cavity, fingers or nose), c) visceral involvement such as pulmonary, hepatic or CNS arteriovenous malformations (AVMs), and d) an affected first degree relative according to these criteria [6,7].

Definite HHT is diagnosed in patients where three criteria are present, in patients with two criteria, HHT can only be suspected. The most common clinical manifestations of HHT are spontaneous recurrent nose bleeds from telangiectasia of the nasal mucosa that are present in more than 90% of all HHT patients. Telangiectases of the skin and buccal mucosa occur in about 75% of individuals with the disease. Hepatic and pulmonary involvement is present in 30% of HHT patients each while gastrointestinal manifestations of the disease occur in approximately 15% [8]. It is estimated that approximately 10%-20% of all HHT patients have CNS involvement [9] consisting of three types of neurovascular malformations, i.e.: arteriovenous fistulae (AVFs), small arteriovenous glomerular or nidus-type malformations (AVMs) and micro AVMs. The most common reason for neurological symptoms in patients with HHT are stroke, transient ischemic attack, and brain abscess that represent complications of pulmonary arteriovenous malformations caused by bland or septic emboli passing through the abnormal fistulous communications in the lungs.

Only approximately one third of neurological symptoms including seizures, hydrovenous disorders and intracranial haemorrhage, are due to cerebral or spinal vascular malformations [10]. Concerning cerebrovascular manifestations of HHT, the disease displays an age-related expression with manifestations developing throughout life and varying between affected individuals, even individuals from the same family. While AVF are present almost exclusively in the age group of young children under five years of age, small AVMs are present predominantly in the population of young adolescents whereas micro AVMs are present in young adults. Because of their vascular phenotypes, children with CNS manifestations of HHT have a poor prognosis: the haemorrhage rate is 1.4-2.0% per year comparable to figures in the non-HHT cerebral AVM population [11,12].

The cumulative risk of a child with HHT and diagnosed with a cerebral AVM to bleed therefore reaches nearly 100%. Moreover, the fistulous AV malformations in the brain or spine can lead to substantial shunting resulting in systemic cardiac failure and cyanosis. Spontaneous thrombosis of the often associated venous pouch may lead to an acute neurological deficit [10,13].

Venous congestion due to the abnormal draining pattern may result in venous ischemia resulting in cortical damage. Finally, spinal manifestations of HHT may lead to haematomyelia with acute tetraplegia. Various therapies for spinal and cerebral arteriovenous malformations have been put forward including surgical resection, stereotactic radiosurgery, embolization, or a combination of these treatments. In the present article we present a single centre experience of endovascular treatment of these lesions to define the therapeutic efficacy, complications and results of endovascular therapies in HHT. To the best of our knowledge, this is the largest consecutive series of treated children with neurovascular manifestations of HHT reported thus far.

Methods

After a retrospective analysis of the databank of the Hôpital Bicêtre from 1989 to January 2005, we selected from all patients with CNS arteriovenous malformations (including brain and spinal cord) those patients that met at least two of the Curaçao criteria [7]: a) spontaneous recurrent nosebleeds, b) mucocutaneous telangiectasia at characteristic sites (lips, oral cavity, fingers or nose), c) visceral involvement such as pulmonary, hepatic or CNS arteriovenous malformations (AVMs), and d) an affected first degree relative according to these criteria. Using these criteria, a total of 52 patients were diagnosed with HHT. Of those there were 39 children under the age of 16 at the time of presentation and of those a total of 31 patients were embolized in our department. Their files that in all cases also included follow-up reports were reviewed according to clinical presentation, family and personal history and follow-up results including neurological status.

The angiographic images before the intervention were analysed with respect to the number of lesions (single, multiple), the location (superficial supratentorial, deep supratentorial, infratentorial, spinal) and type of lesion (fistulous AVM, nidus-type AVM, micro AVM). MicroAVMs were assigned to those lesions where the diameter of the nidus was 1cm or less. Superficial lesions included all AVMs that involved the cortex irrespective of their deep extension according to previous descriptions [14,15]. In addition, the angiographic films were evaluated for any associated angioarchitectural peculiarities such as: venous ectasia or stenosis, pial reflux, transdural arterial supply or associated arterial aneurysms. CT and MRI were analysed for signs of old or new haemorrhage, venous thrombosis, venous ischaemia, calcifications, atrophy, hydrocephalus, and tonsillar prolapse. Angiographic films after the intervention were reviewed according to the number of vessels embolized, and the morphological result, both the films and the report were used to evaluate possible complications.

All children reported were treated employing transarterial superselective embolization via a femoral access route under general anaesthesia. The embolizing agent was N-butyl cyanoacrylate (NBCA) in all 31 children, in one child, platinum coils and fibered coils were used additionally. NBCA (glue) was chosen as embolizing agent since, once stable, total obliteration can be achieved. If more than one session was necessary, the sessions were usually between six and 12 months apart.

Results

This is a consecutive series of 31 children harbouring a total of 46 neurovascular malformations with an age of onset of symptoms between birth and 16 years (mean age of onset: 6.3 years, mean age at presentation: 7.8 years) There was a male preponderance of 19:12. Twenty children presented with 28 arteriovenous (AV) fistulae: seven children presented with spinal AV fistulae and 14 children harboured cerebral AV fistulae (one child had both a spinal and cerebral fistulae), 11 children had small nidus type AV malformations, in two patients a total of four micro AVMs were found. Multiplicity of vascular malformations was found in ten out of 31 children. A total of 111 feeding vessels were embolized in 79 single sessions resulting in a mean overall occlusion rate of the malformation of 76.5% (ranging from 30 to 100%). Clinical follow-up ranged from three to 300 months (mean: 72 months). Two patients (6.5%) died as a direct complication of the embolization procedure, two patients (6.5%) had a persistent new neurological deficit, eight patients (26.7%) were clinically unchanged following the procedure, in eleven patients (36,7%) an amelioration of symptoms could be achieved and six patients (20%) were completely asymptomatic following the endovascular procedure. In the surviving patients morphological complete occlusion was possible in eleven patients (40%), therapy is still not complete in six patients. During follow-up management (mostly due to recurrent epistaxis), we have seen no vascular malformation appear de-novo in our patient population.

Spinal Cord Manifestations

Seven spinal cord AVFs were found in seven patients (figure 1). Patients harbouring this disease were between one month and six years of age, with a mean age of 2.2 years. Six patients had only spinal cord lesions whereas one patient had in addition two infratentorial AV fistulae. Presenting symptoms were acute tetra or paraplegia in five patients due to haematomyelia, progressive tetraplegia due to venous congestion in one patient and spinal subarachnoid haemorrhage in one patient. All spinal

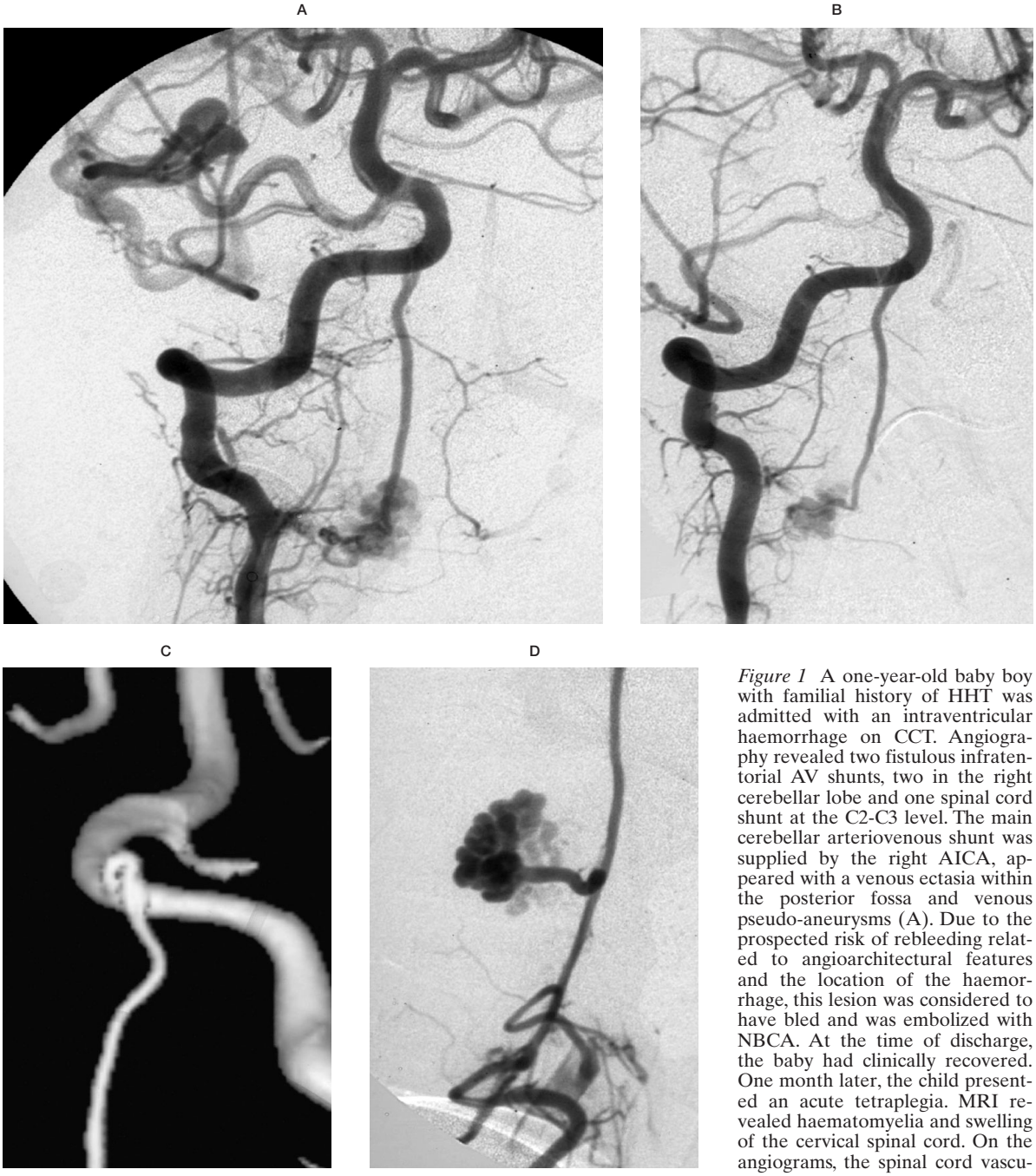
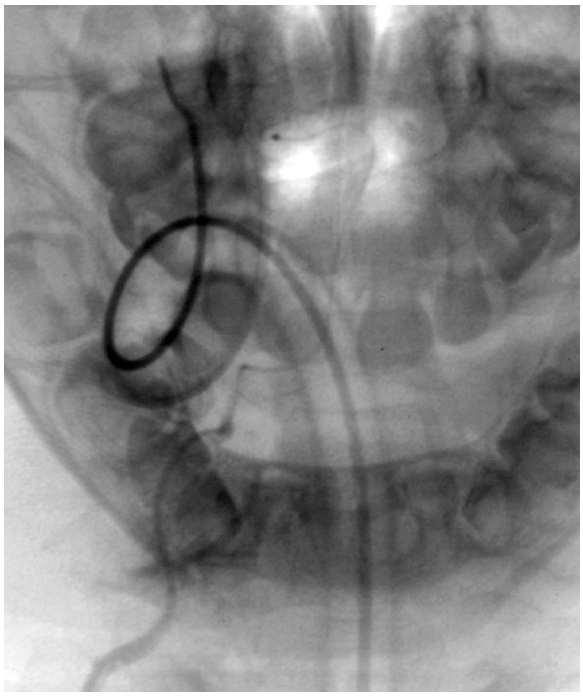


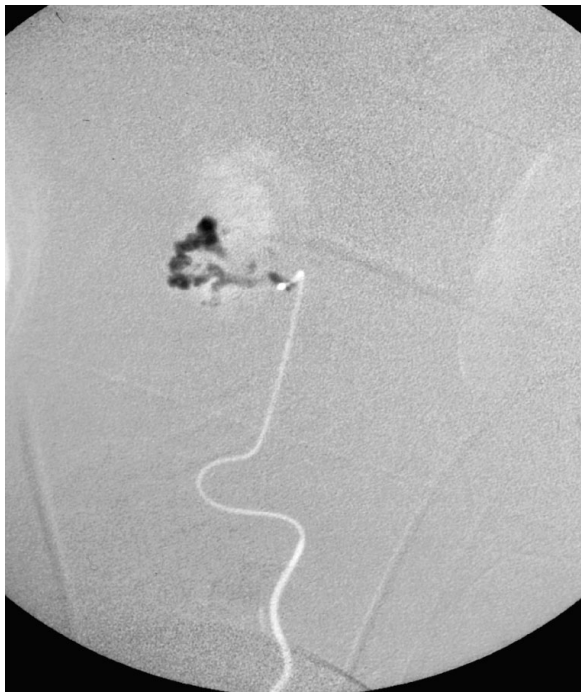
Figure 1 A one-year-old baby boy with familial history of HHT was admitted with an intraventricular haemorrhage on CCT. Angiography revealed two fistulous infratentorial AV shunts, two in the right cerebellar lobe and one spinal cord shunt at the C2-C3 level. The main cerebellar arteriovenous shunt was supplied by the right AICA, appeared with a venous ectasia within the posterior fossa and venous pseudo-aneurysms (A). Due to the prospected risk of rebleeding related to angioarchitectural features and the location of the haemorrhage, this lesion was considered to have bled and was embolized with NBCA. At the time of discharge, the baby had clinically recovered. One month later, the child presented an acute tetraplegia. MRI revealed haematomyelia and swelling of the cervical spinal cord. On the angiograms, the spinal cord vascu-

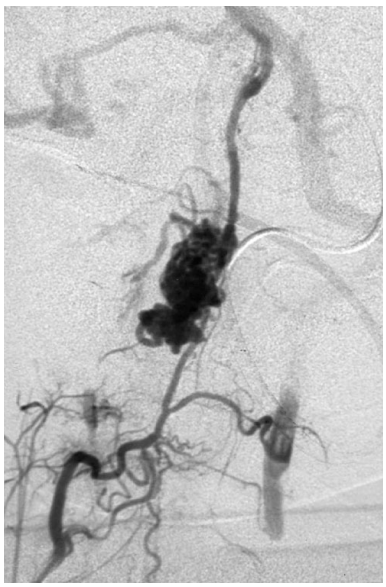
cord AVFs were located on the surface of the cord directly connecting the anterior or posterior spinal artery with medullary veins. Venous ectasias, stenoses and pial reflux were present in all seven patients. Morphological results following glue embolization were very good in all seven patients with 90-100% occlusion in all cases. The clinical result was unchanged in five patients, the patient with the venous congestion showed a marked amelioration of his symptoms and the patient with the spinal SAH was asymptomatic following the intervention.

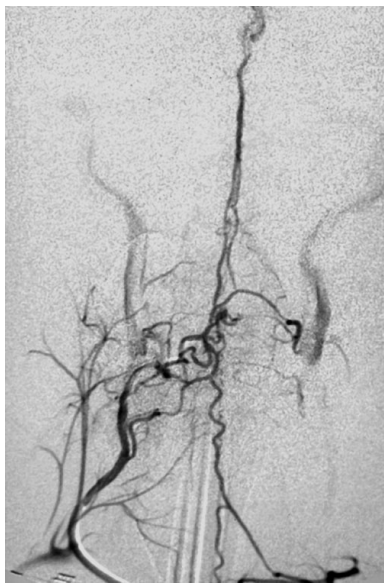
Cerebral AV Fistulae

Twenty-two cerebral AV fistulae were found in 14 patients (figure 2). Age at presentation ranged from birth to ten years, the mean age









lar malformation was supplied by a ventral coronal branch of the anterior spinal artery. The approach through the vertebral artery origin to the anterior spinal artery was felt to be too difficult (C), therefore an approach via the ascending cervical contribution was chosen (D,E), the branch was catheterized and embolized with NBCA (F). During the same session, the second cerebellar AVS was embolized and completely excluded. Embolization with subsequent administration of steroids (1 mg/kg for four days) improved the neurological deficit within one month, with almost normal strength on upper limbs despite persistent sphincter dysfunction and lower limbs paresis. Long term follow-up (H) shows the normalization of the spinal cord supply. The three year follow-up showed significant clinical changes with improvement of the neurological deficits.

was 2.3 years, all patients but one were less than six year old. In our series there was one patient with an AVF and an associated micro AVM, one patient who had an associated spinal cord AVF and no patient with an AVF and an AVM. Multiplicity of AVFs was present in seven out of 14 patients with two to three distinct AV fistulae. Localisation of the AVF was cortical supratentorial in 59% (13/22) and infratentorial in the remaining cases. Presenting symptoms were intracerebral haemorrhage in six patients, macrocrania in four patients, a bruit in three, cognitive deficits and cardiac insufficiency in two patients each, and epilepsy, tonsillar prolapse, and hydrocephalus in one patient each. Only one of 14 patients was clinically asymptomatic, diagnosis was made antenatally. Associated angiographic abnormalities included ve-

nous ectasias (in 12 of 14 patients), venous stenoses (in five out of 14 patients), pial reflux (in three out of 14 patients), venous ischaemia in two patients, calcifications and an associated arterial aneurysm in one patient each. Morphological results after embolization varied between 50 and 100% occlusion rate (mean 85%). Clinically, three patients were completely free of symptoms, seven patients showed amelioration of their symptoms, three patients remained clinically unchanged and one patient died (see paragraph on complications).

Nidus-type and micro-AVMs

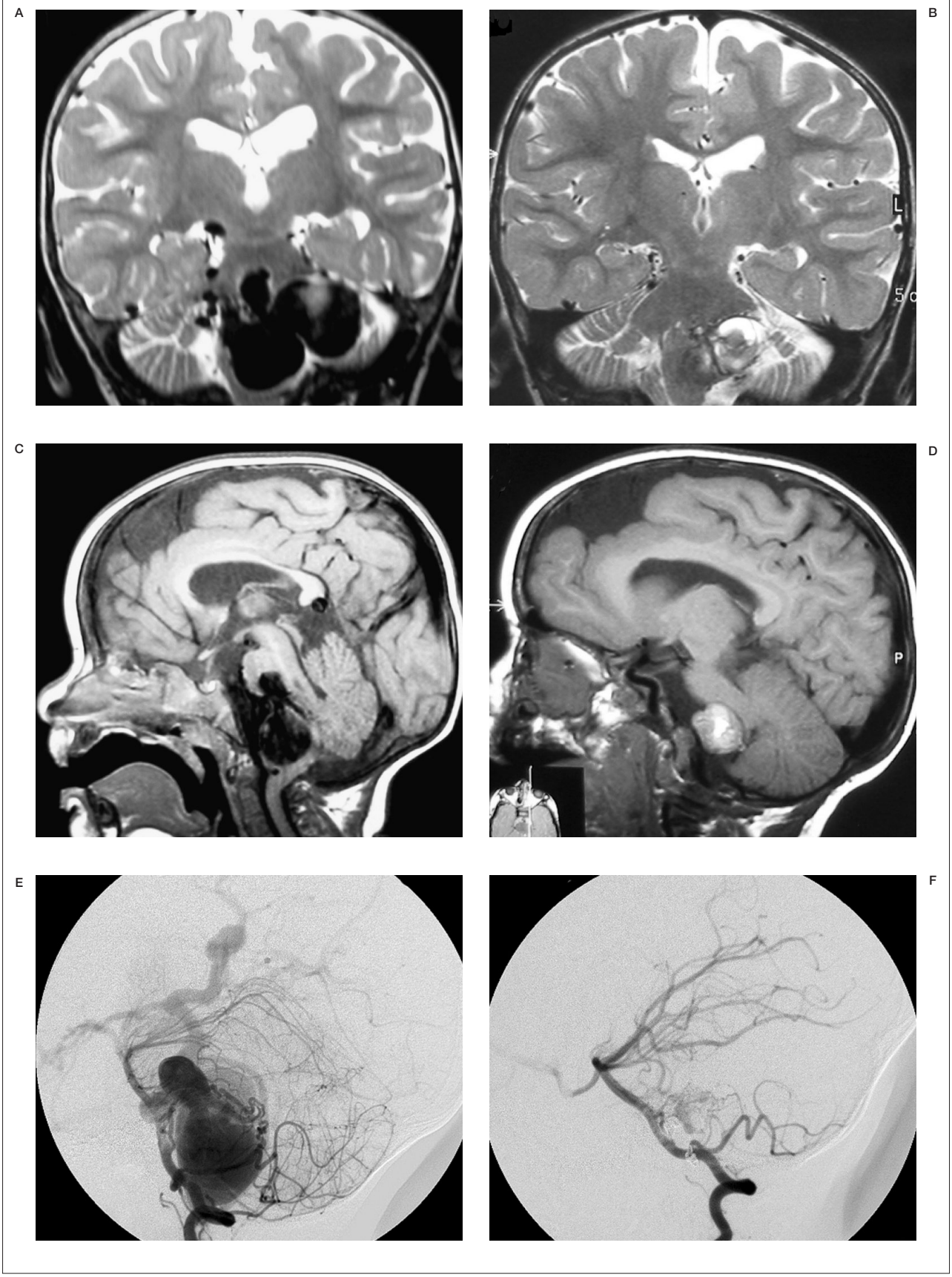
Twelve nidus type AVM were found in eleven patients whose ages ranged from six to 16 years (mean: 12.7). Muliplicity of nidus type AVMs was encountered in one patient, whereas two patients harboured in addition to their nidus type AVM also micro-AVMs (one of them had three, one a single micro-AVM). Size of the nidus type AVM was in all cases between 1 and 3 cm (small AVMs), the micro AVMs had a nidus size of less than 1 cm. Localization of these vascular malformations was cortical in ten out of 13 cases (77%) and infratentorial in the remaining three cases, no deep seated AVMs were encountered, all micro AVMs had a cortical location. While the micro AVMs were asymptomatic in both patients, patients with nidus-type AVMs presented with haemorrhage (6/11 patients), headaches (4/11), epilepsy (3/11), cognitive impairment or macrocrania (one patient each). One patient was clinically asymptomatic. During therapy, only nidus-type AVMs were targeted, micro-AVMs were not embolized. Morphological results after embolization varied between 30 and 100% occlusion (mean 58%). Clinically, three patients were completely free of symptoms, four patients showed an amelioration of symptoms, one patient remained clinically unchanged, two patients experienced a new neurological deficit and one patient died (for the latter three patients see next paragraph). In the follow-up, no microAVM became symptomatic.

Complications

Two of the 31 patients (6.5%) died as a direct complication of the embolization procedure, one patient five hours, the other patient 17 hours after embolization was finished due to a massive intracerebral haemorrhage that was in both cases most likely due to glue embolization with subsequent occlusion of a vein responsible for draining the normal cortex. Two other patients (6.5%) had a persistent new neurological deficit, one patient following a pontine ischaemia that occurred during embolization of an AVM of the brain stem, the other patient's deficit was secondary to a central ischaemia that occurred during embolization of a left frontal AVM.

This patient developed a right hemiparesis affecting mainly the upper limb, after steroid therapy and physiotherapy the patient improved over the next few days to a power of 4/5 on day of discharge. On follow-up one year later, her neurological status remained stable. In one patient a frontal brain supplying artery which branched off close to the point of fistulation could not be spared during embolization. However, the proximal occlusion of this vessel was non-symptomatic, due to good leptomeningeal collateralisation; the control MRI demonstrated no new ischaemia. In one patient, during injection of contrast a slight extravasation of contrast medium was visible, but was immediately be secured with a glue injection.

Figure 2 A one-year-old baby girl with a family history of HHT harboured two distinct cerebellar high-flow AV fistulae of the posterior fossa with giant venous pouches. Images A, C and E represent T2 and T1 weighted images and the DSA run of the left vertebral artery preinterventionally, whereas frames B, D, and F demonstrate the postinterventional images. Preinterventional angiography demonstrated one fistula that was fed by the left PICA and that drained via the lateral mesencephalic vein into the basal vein of Rosenthal leading to a major venous congestion of both the supra- and infratentorial veins and the veins of the spinal cord (Frame C demonstrates the dilated supra- and infratentorial veins). A second fistula was fed by the left AICA and was only visualized after embolization of the first. This fistula demonstrated a separate venous pouch that subsequently drained into the internal cerebral veins. Due to the high flow of the fistula, we decided to first reduce the flow using fibered coils and subsequently embolized the remaining fistula with NBCA resulting in a near complete occlusion of both fistulae. Most importantly, however, venous congestion diminished markedly on follow up. MRI demonstrated progressive thrombosis of the venous pouches, a normalisation of the size of the draining veins and a normal cortical development. The compressive effect on the brain stem and the left cerebellar hemisphere also regressed. Since the child was neurologically intact, the size and volume of the persisting shunt was small and no venous congestion was present, further therapy was not considered necessary at this moment. The child is closely followed with annual MRIs.


A
B
C
D
E
F

On clinical follow-up no new neurological deficits were present, and follow-up MRI showed no defect. Gluing of the catheter occurred in one patient and was well tolerated without any ischaemic events in a follow-up period of now 15 years.

In another patient, a droplet of glue remained at the catheter tip, this prevented the catheter being removed through the sheath. The patient went to vascular surgery where the catheter was removed without any further complications. One patient with an AV fistula associated with a large venous pouch had a transient central motor deficit (most likely due to venous congestion) that completely regressed during hospitalisation, the patient was free of any symptoms in the further follow-up. In our series, two deaths that were not related to the embolization occurred: one patient died 14 months after embolization secondary to an ischaemic stroke from an untreated associated pulmonary fistula.

One patient died four years after embolization of a right-sided AVM following massive intracerebral haemorrhage of a known left-sided AVM that had not been treated due to technical difficulties.

Discussion

Imaging Appearances and Angioarchitecture

On MRI, neurovascular phenotypes of HHT typically appear as areas of serpiginous flow voids insinuating into the brain parenchyma. Patients often have multiple malformations of varying types, many of which have an atypical or indeterminate MRI appearance. Most often, the lesions are located near the surface of the brain. As pointed out by Fulbright and coworkers, MRI might underestimate HHT-related vascular malformations, however, the large (and potentially dangerous) lesions such as arteriovenous malformations and AV fistulae are readily detectable on routine sequences [9]. The micro AVMs on the other hand might remain unnoticed on MRI, but do not tend to bleed in the HHT population [15,16]. Therefore, MRI might constitute an appropriate method for screening patients with HHT for neurovascular manifestations. Cerebral angiography is required for diagnosis of equivocal lesions and for treatment planning since complete angioarchitectural analysis is important for defining the therapeutic strategy.

There are different types of vascular malformations associated with HHT: Cerebral arteriovenous fistulae (AVF) are typically pial lesions with a direct shunt (i.e. no nidus), with a huge ectactic draining vein, most arteries feeding a pial AVF open into a single draining vein [15,16].

Spinal AVFs typically connect the anterior or posterior spinal artery directly with medullary veins. These large AVFs are always located on the surface of the cord. The single hole AV fistulas are in our opinion such a classic finding for HHT, that based on our experience, they should be added as a fifth criterion to the four well established Curaçao criteria.

Other types of HHT-related vascular malformations are the small arteriovenous malformations (AVMs) with a nidal size between 1 and 3 cm and the micro AVMs with a nidus smaller than 1 cm [15,16,17]. These AVMs typically demonstrate only one single draining vein and are almost exclusively located near the cortex [15]. Whereas micro AVMs do not show a tendency to bleed, small AVMs do. There is a high incidence of multiplicity of vascular malformations in the HHT population compared to the non-HHT population.

Age Relation

We have found an age-related expression of the above mentioned neurovascular phenotypes in HHT, with manifestations developing throughout life and varying between affected individuals, even individuals from the same family [18]. While AVF were present almost exclusively in the age group of young children under five years of age, small AVMs were present predominantly in the population of adolescents whereas micro AVMs were present in young adolescents. These findings are in line with other studies that also demonstrate an age related phenotypic appearance of neurovascular manifestations of HHT. Matsubara et Al studied 14 patients with HHT and evaluated the angiographic pattern of the cerebral lesions. They found 28 cerebral AVMs, eight of them being of the fistulous type and occurring exclusively in children under 15 years of age. The 12 micro AVMs were equally distributed in patients under and over 15 years of age (six each), whereas of the eight small AVMs seven occurred in adults [15]. Mahadevan et Al evaluated 39 patients with HHT but did not specifically look at the age distribution of the different phenotypical appearances [16]. Fullbright et Al reported on

the thus far largest group of patients with HHT, but they mainly focussed on MRI and performed angiography only in a small number of cases. Moreover, no details concerning the age relation are given [9].

In several studies with fewer patients, only specific aspects of this disease such as the posterior fossa supratentorial single hole AV fistulae in children [13], pial AV fistulae as presenting manifestation in children [10], multiplicity of cerebral AVMs [19] or the combined occurrence of spinal and cerebral arteriovenous malformations [20] have been studied intensively. The common element of these studies is that AV fistulae occur in young children whereas micro and small AVMs typically occur later in life. Although little is known on the exact pathogenesis, one might presume that the age dependence might be related to the timing of the revealing triggering event. Blood vessels undergo a complex vasculogenesis and angiogenesis, especially during perinatal life and infancy, with vessels being continuously renewed. Therefore, blood vessels cannot be regarded as being the same throughout life or harbouring identical repair capacities or a similar strength. Instead these factors may vary with age. This might lead to the hypothesis that although the different phenotypical manifestations of HHT are due to the same genetic defect they depend on the timing of the revealing trigger [21]. Micro AVMs, small AVMs and large single hole fistulous AVMs might therefore be regarded as a continuous phenotypical spectrum of a destabilized capillary-venous bed.

Therapeutic Strategies

There is paucity of data on the risk/benefit ratio of presymptomatic intervention for the different neurovascular manifestations of HHT [22]. Although there is general agreement that micro AVMs should not be treated since they do not tend to bleed [15,16], the question on the risk/benefit ratio of treating the other types of vascular HHT manifestations requires further attention. Management approaches across different countries differ markedly. Screening procedures are not undertaken in the majority of European centres. Morbidity following rupture of a cerebral AVM is quoted to be between 53 and 81% in the non-HHT population [12], and there is no suggestion that this should differ in the HHT population [22]. It has been put forward, though, that there is a lower rate of haemorrhage in the vascular malformations associated with HHT compared to the sporadic cerebral AVMs in the non-HHT population [23]. This still remains a matter of debate, since in a retrospective study that collected data from 22,061 years of HHT patient life, Easey and colleagues found out that the haemorrhage rate of HHT patients resembles that of the non-HHT cerebral AVM population, being between 1.4 and 2.0% per annum per patient with a preponderance for male subjects [22]. These high rates of bleeding contradict other authors who reported a haemorrhagic risk of less than 1% in Dutch and American HHT populations [23,24], but these studies might have been biased by not spanning the outcome over the patient's whole life. In a recent study of Morgan and coworkers [25], the authors stated that infants and children are especially at risk for sudden intracranial haemorrhage. They concluded that screening for neurovascular manifestations of HHT should be performed in all affected patients with the goal of presymptomatic intervention.

Bleeding is not the only serious risk associated with the cerebral vascular malformations present in HHT patients: neurological deficits due to venous congestion, venous ischaemia, spontaneous partial thrombosis with acute neurological deficits, subarachnoid haemorrhage, congestive cardiac failure, hydrocephalus, macrocrania and brain atrophy are other grave complications that might occur in untreated neonates and infants and lead to a poor prognosis of untreated children [10].

Pial AV shunts in particular might interfere with normal postnatal brain development. In addition, untreated spinal cord AV shunts have a grim prognosis as demonstrated in our series, since many spinal cord AV shunts became symptomatic with acute haemorrhage and tetraplegia. It has to be noted, that in the adult population, fistulous lesions are never encountered. This indicates either a spontaneous regression, which is rather unlikely, or a deleterious effect before adulthood providing another argument for the high morbidity and mortality of these lesions. The devastating effects of haemorrhage, the hydrovenous disorder with its potential complications, and the need for maturation of the venous system, therefore might lead to presymptomatic intervention, which, however, is only justified, if the risk reduction outweighs the procedural morbidity. Up to now, there have been no larger series on

the morbidity and mortality of treatment in HHT patients to clarify the procedural morbidity. Due to the paucity of data and the complexity of these malformations, there are no established management strategies at present, and, to the best of our knowledge, except for occasional case reports, there are no large patient series on treatment of neurovascular manifestations of HHT in the literature. However, given the above mentioned considerations, it is our opinion that the neurovascular manifestations of HHT (apart form the micro AVMs) should be treated, even if they are (at the time of presentation) asymptomatic. There are three different treatment strategies: surgery, radiosurgery, and embolization.

The risk of surgical excision of arteriovenous malformations depends on the size of the lesion, the venous drainage pattern (superficial versus deep) and the lesion location resulting in the so-called Spetzler-Martin classification. Mortality of surgery in low Spetzler-Martin grades approaches nearly 0% with a high cure rate, whereas mortality may be as high as 20% for midbrain AVMs [26,27,28]. However, this score applies to one surgical team and is not necessarily applicable to children. Concerning pial AV fistulae, open surgery and endovascular obliteration have proved to be of equal effectiveness [10], but the endovascular approach avoids craniotomy and shortens the hospital stay.

Radiosurgery of small cerebral AVMs leads to a progressive occlusion over the course of typically two years, the mortality of the radiotherapy is low, i.e. 3%, however, a recent study by Fleetwood and Steinberg suggests that radiosurgery cures only 65-85% of all patients [26]. Moreover, there are no data on radiosurgery of fistulous AVMs with giant venous pouches as often present in the HHT population. One might presume that the large communication between artery and vein in the fistulous zone of these lesions might prevent radiosurgical success. Radiosurgery of spinal lesions is not possible. A recent review suggests that patients after radiosurgical management fared less well in terms of immediate mortality, obliteration of the lesion and postinterventional neurological outcome compared to patients treated by microneurosurgery [27].

There is a much experience on the treatment of AVFs, AVMs and spinal AV fistulae in the non-HHT population with endovascular techniques. Although four patients died in our series, only two died as a direct consequence of the embolization, the other death was related to bleeding of an untreated AVM and the other due to an embolic stroke from a pulmonary AV fistula. We therefore strongly recommend screening the lungs to rule out pulmonary involvement and embolization of all arteriovenous malformations and fistulae. In our experience, even partial targeted embolization was found to be of benefit for the patient [13,16]. In a total of 19 children in whom the malformation was not completely embolized we have 909 months of follow-up. There has been no rebleed up to now which highlights the beneficial effects of a partial, targeted embolization only. However, up to now, no trials have directly compared embolization with other forms of treatment.

In addition, there has been no large series on the treatment of the specific neurovascular manifestations of HHT patients. In our series of 31 consecutive patients we found that embolization carries a 6.5% risk of new permanent neurological deficits and a 6.5% mortality rate. Given the above mentioned data concerning the natural history of this disease and the fact that nearly 60% of patients improved or were cured following embolization, we think that embolization in specialized centres is a sound treatment option.

Still, for each individual patient and lesion type a specific risk assessment must be made considering the angioarchitecture of the lesion, the patient's age, and the experience of the available centre for a specific therapeutic regimen. Treatment goals should be twofold: a) to provide stable protection from haemorrhage or progressive neurological deficits, and, b) to preserve normal cognitive maturation. To reach these goals, our centre favours partial targeted and staged treatment after careful angioarchitectural analysis.

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